Nicolaides–Baraitser syndrome in a patient with hypertrophic cardiomyopathy and SMARCA2 gene deletion

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Abstract

Nicolaides–Baraitser syndrome is a rare, neuro-developmental disorder caused by heterozygous pathogenic variants in the SMARCA2 gene, involved with chromatin regulation. Cardinal features include intellectual disability, short stature, microcephaly, triangular facies, sparse hair, brachydactyly, prominent interphalangeal joints and seizures. Genetic testing demonstrated a loss within SMARCA2 at 9p24.3 inclusive of basepairs 2094861_2141830 (hg19) in our patient. This case highlights a child with Nicolaides–Baraitser syndrome, a SMARCA2 gene deletion and a novel association of hypertrophic obstructive cardiomyopathy.

Case presentation

A baby boy was born at full term, the product of non-consanguineous parents. A diagnosis of intrauterine growth restriction was made antenatally, and he weighed 2.3 kg at birth. He had an uncomplicated delivery with no respiratory distress and normal vital signs. However, he was noted to have significant feeding difficulties and a harsh grade 3/6 systolic murmur in the early neonatal period. Nasogastric tube feeding was initiated and an echocardiogram was carried out within the first week of life to investigate. This demonstrated situs solitus with normal cardiac connections and severe hypertrophic obstructive cardiomyopathy with asymmetric hypertrophy and dynamic intracavity obstruction. The pulmonary valve was mildly dysplastic with no significant gradient. Propranolol therapy was initiated at a dose of 1 mg/kg three times a

Figure 1. (a) Clinical photograph of child with Nicolaides–Baraitser syndrome, demonstrating coarse facial features with a triangular-shaped face, sparse hair and downward slanting palpebral fissures. (b) Characteristic hand features including brachydactyly and prominent interphalangeal joints.
metric septal hypertrophy with left ventricular outflow tract obstruction. The SMARCA2 gene provides energy to the SWI/SNF complex for this achieve by repositioning or removing nucleosomes. The tightly packed DNA reduces gene expression. SWI/SNF proteins DNA allows for higher levels of gene expression, whereas more remodelling is a way of regulating gene expression. Loosely packed age long strains of DNA into more complex structures. Chromatin is the complex of DNA and proteins used to pack-

Discussion

The SMARCA2 gene, also known as hBRM, is located on chromosome 9p24.3 and contains 38 exons. It encodes the core ATPase catalytic subunit of the main human BRM-associated factors complex which belongs to the SWI/SNF group of protein complexes. These complexes regulate gene expression via chromatin remodelling. Chromatin is the complex of DNA and proteins used to package long strands of DNA into more complex structures. Chromatin remodelling is a way of regulating gene expression. Loosely packed DNA allows for higher levels of gene expression, whereas more tightly packed DNA reduces gene expression. SWI/SNF proteins achieve this by repositioning or removing nucleosomes. The SMARCA2 gene provides energy to the SWI/SNF complex for this process using ATP. SWI/SNF complexes regulate gene expression in many different processes including cell growth and division, and DNA repair and replication.

Nicolaides−Baraitser syndrome was first described in 1993 but has only recently been well delineated. At least 50 mutations in the SMARCA2 gene have been identified and associated with Nicolaides−Barrister syndrome. Almost all of these mutations are a missense or loss of function single nucleotide variants in the SMARCA2 gene. Interestingly, our patient was found to have the less frequently described deletion within the SMARCA2 gene. All of the identified mutations occur in the region of the SMARCA2 gene which encodes the ATP binding region. The resulting altered protein cannot bind to ATP and therefore cannot provide energy to the SWI/SNF complex for chromatin remodelling. Loss of function of the SWI/SNF complexes results in multi-systemic complications, since these complexes regulate gene expression in a large number of processes throughout the body.

Phenotypically, the main features of Nicolaides−Baraitser syndrome include typical triangular facies, sparse hair, microcephaly, severe intellectual disability, epilepsy, short stature, brachydactyly and prominent interphalangeal joints. Other abnormalities including ophthalmological, audiological and gastrointestinal have been identified. In a complete analysis of all confirmed cases (61) in 2014, 6 were found to have cardiac involvement. Atrial septal defects, patent ductus arteriosus, double aortic arch, mild pulmonary stenosis, mild self-resolving left ventricular hypertrophy, mild aortic coarctation and tracheal compression of the trachea by the brachiocephalic trunk were all described (Table 1). However, to our knowledge, we report the first case of hypertrophic obstructive cardiomyopathy in a patient with confirmed Nicolaides−Baraitser syndrome.

This is the first report of hypertrophic cardiomyopathy occurring in the setting of Nicolaides−Baraitser syndrome. Although the hypertrophic cardiomyopathy gene panel was negative in this patient, one may postulate that loss of function of the SMARCA2 gene may be associated with the development of hypertrophic 

![Image](https://doi.org/10.1017/S1047951121003826) Published online by Cambridge University Press
cardiomyopathy in this patient. This report highlights the need to assess for cardiomyopathy in Nicolaides–Baraitser syndrome.

**Conclusion**

This is the first case to our knowledge which describes hypertrophic obstructive cardiomyopathy in association with Nicolaides–Baraitser Syndrome. As the phenotype of this rare disease is still being described, we hope this case will add to the current available knowledge in the literature.

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**References**